

# Iatrogenic and spontaneous late preterm twins – which are at higher risk of neonatal complications?

Jatrogenne i samoistne późne wcześniactwo wśród bliźniąt a ryzyko powikłań noworodkowych

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## Abstract

**Objectives:** To evaluate data regarding neonatal mortality and short term morbidity among iatrogenic late preterm (ILP) and spontaneous late preterm (SLP) twin births, and to estimate whether medical interventions – induction of labor in this particular context, are associated with better or poorer outcomes.

**Material and methods:** Retrospective analysis of 110 late preterm dichorionic twin pregnancies was performed basing on medical charts data. All twins were delivered in years 2005-2011 at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw. Late preterm twins, defined as those delivered between 34+0-36+6 weeks of gestation, were divided into spontaneous and iatrogenic preterm births. The primary outcomes of the study were various neonatal adverse events, including one of the following per pregnancy: admission to Neonatal Intensive Care Unit (NICU), respiratory disorders (RD) and pneumonia, intraventricular hemorrhage (IVH), sepsis, NEC and jaundice requiring phototherapy. Mann-Whitney U-test and chi-squared test were used and logistic regression performed to calculate odds ratio, with  $p$  value < 0.05 considered significant.

**Results:** There were 69 (62.7%) spontaneous and 41 (37.3%) iatrogenic late preterm twins. There were no differences in maternal characteristics, mode of delivery and newborns' Apgar scores. The mean birth weight did not differ significantly between the groups. There was one case of perinatal death of one twin in ILP group. Preeclampsia (31.7%) and IUGR (17%) were the most frequent indications for labor induction in ILP. Women in the ILP group were administered steroid treatment for lung maturation more frequently than SLP group due to pregnancy complications (73.17% vs. 30.44%;  $p < 0.0001$ ). Nevertheless, ILP twins were at higher risk of respiratory disorders (41.46% vs. 15.94%;  $p = 0.003$  – significant either with or without pneumonia) and NICU admission (31.71% vs. 14.49%;  $p = 0.032$ ) than SLP twins. The only two independent factors influencing the occurrence of poor neonatal outcome were gestational age in weeks (OR 0.57; 95% CI 0.34-0.94) and preeclampsia (OR 5.01; 95% CI 1.51-16.67). In the additional analysis of gestational age odds ratio, only the delivery at 34 weeks of gestation increased the incidence of adverse neonatal outcome almost five times (OR 4.94, 95% CI: 1.64 – 14.88). The rate of cesarean delivery in the SLP was 81.61%, while in the ILP it reached 90.23% ( $p = 0.17$ ).

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**Conclusions:** Late prematurity in twin pregnancies is associated with higher risk of neonatal morbidity than in term twins. Iatrogenic late preterm birth increases the risk of NICU admission and respiratory disorders in neonates in comparison to spontaneous late preterm birth. Despite the fact that respiratory complications are generally mild and mostly temporary, there is a need for careful evaluation of indications for delivery in that particular group.

Key words: **late preterm births / twin gestation / neonatal mortality / neonatal morbidity / respiratory disorders /**

## Streszczenie

**Cel pracy:** Analiza śmiertelności oraz krótkoterminowej zachorowalności noworodków urodzonych wskutek samoistnych i jatrogennych późnych porodów przedwczesnych w ciążach bliźniaczych.

**Materiał i metodyka:** Retrospektywną analizą objęto 110 dwukosmówkowych ciąż bliźniaczych, których porody odbyły się pomiędzy 34+0 a 36+6 tygodniem ciąży (tzw. późne wcześniactwo) w I Klinice Położnictwa i Ginekologii Warszawskiego Uniwersytetu Medycznego w latach 2005-2011. Grupę badaną podzielono na samoistne (SLP) i jatrogenne (ILP) późne porody przedwczesne, a następnie porównano je między sobą. Głównym punktem końcowym badania były powikłania noworodkowe (przynajmniej jedno na ciążę): przyjęcie do oddziału intensywnej opieki noworodkowej (OION), zaburzenia oddychania i zapalenie płuc, wylewy dokomorowe, sepsa, martwicze zapalenie jelit, żółtaczka wymagająca fototerapii. W analizie statystycznej posłużono się testem Mann'a-Whitney'a i  $\chi^2$  oraz analizą regresji w celu wyliczenia ilorazów szans. Za poziom istotności statystycznej przyjęto  $p < 0,05$ .

**Wyniki:** Nie stwierdzono żadnych różnic pomiędzy grupami w odniesieniu do charakterystyki matek, sposobu porodu oraz stanu urodzeniowego noworodków. Najczęstszymi powikłaniami ciąży prowadzącymi do indukcji późnego porodu przedwczesnego w grupie jatrogennej był stan przedrzucawkowy (31%) oraz hipotrofia płodu (17%). Bliźnięta ILP miały większe ryzyko powikłań oddechowych niż bliźnięta SLP (41,46% vs. 15,94%), jak również częściej były przyjmowane do OION (31,71% vs. 14,49%;  $p = 0,032$ ). Jedynymi niezależnymi czynnikami ryzyka powikłań noworodkowych okazały się skończone tygodnie ciąży (OR 4,94 dla 34. tygodnia) oraz stan przedrzucawkowy (OR 5,01).

**Wnioski:** Późne wcześniactwo w ciążach bliźniaczych związane jest z wyższym niż w ciążach donoszonych ryzykiem zachorowalności noworodków. Jatrogenne późne porody przedwczesne zwiększają ryzyko powikłań oddechowych oraz przyjęcia do OION w porównaniu do samoistnych późnych porodów przedwczesnych.

Słowa kluczowe: **późne wcześniactwo / ciąża bliźniacza / umieralność noworodków / zachorowalność noworodków / zaburzenia oddychania /**

## Introduction

Preterm birth (PTB; <37 weeks of gestation) affects approximately 7-10% of all deliveries in Poland and around 12.5% in USA each year [1, 2]. As prematurity is the leading cause of neonatal mortality and morbidity, it has always been a serious problem for healthcare systems worldwide. A few years ago a common obstetrical phrase "near term" was replaced with the term "late preterm birth" (LPTB) to emphasize that neonates born at 34+0 – 36+6 weeks of gestation cannot be treated as term infants, as they are at increased risk of both neonatal mortality and morbidity, not only of respiratory origin [3]. Recently, so called late preterm births have become the topic of much debate and research, as together with moderately preterm births (32+0 – 33+6 weeks) they account for 60-71% of all preterm deliveries [4, 5, 6].

Over the last few decades, the frequency of twin gestations has increased greatly, with the rate of preterm births among them rising from 48 to 60%, and LPTB being the largest group of all [7]. Recently published studies show similar short and long term morbidities in preterm twins [8, 9]. They present an increased morbidity including respiratory complications, neonatal intensive care unit (NICU) admissions, hypoglycemia, temperature instability and feeding difficulties [10].

Since multiple gestations contribute greatly to the group of LPTB, a question arises, whether all the deliveries taking place before 37 completed weeks of gestation are fully justified, which especially concerns iatrogenic deliveries of preterm twins.

## Objective

The objective of the study was to evaluate data regarding neonatal mortality and short term morbidity among iatrogenic late preterm (ILP) and spontaneous late preterm (SLP) twin births. Moreover, it was aimed to estimate whether medical interventions – induction of labor in this particular context, are associated with better or poorer outcomes.

## Material and methods

Data of 263 dichorionic twin pregnancies, delivered at the 1st Department of Obstetrics and Gynecology, Medical University of Warsaw, in years 2005-2011, were retrospectively analyzed. Only late preterm births (110 twins), defined as delivery between 34+0 and 36+6 weeks of gestation, were included for further analysis and divided into spontaneous (69 twins) and non-spontaneous preterm births (41 twins). The SLP birth was defined as a result of primary uterine contractions, while the ILP birth was due to medical indications for the delivery. In case of preterm rupture

of membranes (PROM) with no contractions, antibiotics were administered and laboratory indices of intrauterine infection (leukocytosis and C-reactive protein) monitored. Labor induction or cesarean section was performed if infection parameters were increasing despite antibiotic administration, or fever (defined as temperature above 38 degrees Celsius) was observed. In the above cases they were treated as iatrogenic births. If uterine contractions occurred spontaneously after PROM, they were classified as SLP births.

The primary outcome of the study was at least one of the following per pregnancy: admission to Neonatal Intensive Care Unit (NICU), respiratory disorders (RD) requiring mechanical ventilation / CPAP (continuous positive airway pressure) including pneumonia, intraventricular hemorrhage (IVH), sepsis, NEC or jaundice requiring phototherapy. Maternal characteristics, such as age, parity, pregnancy complications and mode of delivery were compared. Indications for non-spontaneous LPTB were evaluated. Mean birth weights of newborns and their Apgar scores were compared between groups.

The analyses were performed by twin-pair, in which the worse outcome for the pair was considered the outcome of interest. Statistica 10.0 software was used for statistical analysis, with p value <0.05 regarded as significant. Mann-Whitney U-test for continuous variables and chi-squared test for categorical variables were applied and logistic regression performed to calculate odds ratio (OR) where applicable.

## Results

The rate of late preterm twins was 41.83% (110 out of 263). In 69 cases the delivery was spontaneous (62.7% – SLP) and in 41 iatrogenic, due to specific indications (37.3% – ILP). The mean maternal age did not differ between the groups. The rate of primiparas was 60.9% in the SLP and 75.6% in the ILP (p=0.11). The mean maternal pre-pregnancy BMI did not differ significantly between the groups, while the mean weight gain was significantly greater in the ILP. Mean gestational age at delivery was 35.46±0.8 in SLP and 35.29±0.8 in ILP (p=0.2). Characteristics of both groups are presented in Table I.

**Table I.** Maternal characteristics in spontaneous (SLP) and iatrogenic (ILP) late preterm groups.

	mean±SD	min	max	mean±SD	min	max	p
	SLP			ILP			
<b>Age</b>	31.01±4.1	19	43	31.98±3.9	23	41	0.21
<b>BMI</b>	22.49±3.2	17.3	35.78	23.61±4.2	18.63	39.26	0.12
<b>Weight gain</b>	16.33±5.6	5	29	19.53±3.0	2	31	0.001
<b>Weeks of gestation</b>	35.46±0.8	34	36	35.29±0.8	34	36	0.22

BMI – body mass index; SD – standard deviation

**Table II.** Pregnancy complications in the SLP and ILP and indication for delivery in ILP.

	SLP n=69 n (%)	ILP n=41 n (%)	p	ILP – indications for delivery n (%)
<b>GDM</b>	11 (15.94)	4 (9.76)	0.44	0
<b>Preeclampsia</b>	5 (7.25)	13 (31.71)	0.0008	13 (31.71)
<b>PROM*/**</b>	22 (31.88)	3 (7.32)	0.0007	2 (4.88)* / 1 (2.44)**
<b>Intrahepatic cholestasis of pregnancy</b>	3 (4.35)	9 (21.95)	0.004	4 (9.75)
<b>IUGR</b>	4 (5.8)	7 (17.07)	0.53	7 (17.07)
<b>Placental abruption</b>	0	3 (7.32)		3 (7.32)
<b>Intrauterine fetal distress without growth restriction</b>	0	3 (7.32)		3 (7.32)
<b>HELLP syndrome</b>	0	1 (2.44)		1 (2.44)
<b>Fetal demise</b>	0	1 (2.44)		1 (2.44)
<b>Uncertain ***</b>				6 (14.63)

\*premature rupture of membranes with intrauterine infection; \*\*premature rupture of membranes with transverse lower fetus lie;

\*\*\*uncertain indications for delivery; GDM - gestational diabetes; PROM - premature rupture of membranes; IUGR - intrauterine growth restriction

Pregnancy complications in both groups and indications for delivery in ILP are presented in Table II. In 6 cases no evident indication for cesarean section could be identified.

The rate of cesarean delivery in the SLP was 81.61%, while in the ILP it reached 90.23% ( $p=0.17$ ). [*The above rates are high because the breech presentation of either of the twins is an indication for cesarean section in our institution. However, it had no influence on the results, as these rates were equally high in both groups*]. Women in the ILP group, due to various pregnancy complications, were administered steroids for lung maturation more frequently than SLP group (73.17% vs. 30.44%;  $p<0.0001$ ). The mean birth weight of newborns did not differ significantly between the groups. There was one case of perinatal death of one twin in ILP group. More than 90% of newborns from both groups were born with Apgar score  $\geq 7$  at 5 minute. The median Apgar score in the first minute was 10 for both twins in the ILP, while in the SLP it was 10 for the first and 9 for the second twin. There were also no significant differences when rates of neonates born in good, average and bad general condition were compared between groups.

Neonatal complications (analyzed primary outcome) in at least one twin are specified in table III.

Logistic regression analysis was performed to define the impact of analyzed factors on adverse neonatal outcome (defined as NICU admission, sepsis, RD including pneumonia, IVH, NEC, jaundice requiring phototherapy). The only two independent factors influencing the occurrence of poor neonatal outcome were gestational age in weeks (OR 0.57) and preeclampsia (OR 5.01) (see Table IV). In the additional analysis of gestational age odds ratio, only the delivery at 34 weeks of gestation increased the incidence of adverse neonatal outcome almost five times (OR 4.94, 95% CI: 1.64 – 14.88).

## Discussion

Over the last few decades the survival of preterm neonates has improved greatly, mostly due to the advances in clinical management, especially antenatal steroid administration and NICU improvements. Nevertheless, alongside improvements an increasing rate of preterm deliveries has been observed – for example according to US data it increased by 33% from 1981-

**Table III.** Neonatal complications in at least one twin in the ILP and SLP.

Neonatal complications	SLP n=69 n (%)	ILP n=41 n (%)	p
NICU	10 (14.49)	13 (31.71)	0.032
RD	11 (15.94)	17 (41.46)	0.003
pneumonia	15 (21.74)	9 (21.95)	0.98
IVH	18 (26.09)	7 (17.07)	0.27
Sepsis	0	0	
NEC	1 (1.45)	0	0.44
Jaundice requiring phototherapy	12 (17.39)	12 (29.27)	0.22

NICU – Neonatal Intensive Care Unit admission; RD – respiratory disorders requiring mechanical ventilation and/or CPAP other than pneumonia; IVH – intraventricular hemorrhage; NEC - necrotizing enterocolitis

**Table IV.** Risk factors of adverse neonatal outcome.

Analyzed factor	OR	95% CI
Maternal age	0.96	0.87 – 1.06
Parity	0.75	0.4 – 1.41
Weeks of gestation	<b>0.57</b>	<b>0.34 – 0.94</b>
Weight gain	1	0.96 – 1.05
BMI	1.02	0.92 – 1.14
GDM	0.36	0.11 – 1.24
Preeclampsia	<b>5.01</b>	<b>1.51 – 16.67</b>
PROM	0.45	0.16 – 1.21
Intrahepatic cholestasis of pregnancy	0.79	0.23 – 2.7
IUGR	1.97	0.59 – 6.56

2006, mostly because of LPTB [7]. The majority of published studies regarding late preterm births refer to singleton pregnancies. There is no clear explanation for the overall increasing rate of LPTB, therefore several hypotheses appeared in the literature, among them increasing rates of multiples.

The rate of late preterm birth rate among twins is around 45.6% - 49.8% [10, 11]. Our results were also alike – 41.83%. However, the rate of preterm birth seems quite high, considering the recently published RCOG (Royal College of Obstetricians and Gynaecologists) recommendations, advocating birth at completed 37 weeks of gestation for patients with an uncomplicated dichorionic twin pregnancy [12].

The research on late preterm twins is not as extensive as on singletons. Moreover, a respectively small number of papers cover the subject of spontaneous versus induced (also called iatrogenic) LPTB in twins. Respiratory distress syndrome, sepsis, intraventricular haemorrhage, the need for phototherapy or NICU admission are only the most frequently mentioned complications affecting preterm babies [1, 3, 6, 8, 13, 14]. Studies on twin gestations represent similar findings, however the risks of neonatal morbidity and mortality in comparison to singletons are 5 to 8 times higher [3, 10, 11].

Gyamfi et al. suggested the division of indications for preterm delivery into evidence based and non-evidence based [15]. They classified, among others, severe preeclampsia/eclampsia; IUGR with abnormal testing or poor interval growth and cholestasis with bile acids  $>40\mu\text{mol/L}$  as evidence based. Chronic or gestational hypertension/ mild preeclampsia, IUGR with normal testing and adequate interval growth, oligohydramnios and others were among non-evidence based indications, as various studies showed no benefit of earlier delivery either for the mother, or for the neonate in the above cases [15]. It appears that late preterm infants delivered without an evidence-based indication have higher neonatal and infant mortality rates in comparison with spontaneous LPTB babies [6]. It seems to be the group that should be focused on, as the indications can be verified and moderated and expectant management in some cases could be beneficial. On the other hand, evidence based indications most probably will not change in the future. It is understandable that if they occur, the risk of neonatal death is 2 times higher, as reported by Chen et al. [16]. The same refers to neonatal morbidity [9]. The rate of iatrogenic LPTB varies from 20% to 32.3% [5, 15]. In our study it was a little higher and reached 37.27%. Gyamfi et al. found that 56.7% of iatrogenic late preterm deliveries in their material were induced following a non-evidence based, therefore in some way avoidable, indications. They proved that the risk of NICU admission was primarily dependent on early gestational age. The results of our study also showed a similar finding - the delivery at 34 weeks of gestation increased the incidence of adverse neonatal outcome almost five times.

Data published by Reddy et al. suggest a 23% rate of no recorded obstetric or medical indication for early delivery among all LPTB [6]. Their analysis covered 3.5 million births throughout US and pointed out that at 34 weeks of gestation neonatal mortality was around 10 times higher than that of 39 weeks. In our study preeclampsia was the most frequent indication for delivery (31.71%), however, there were definitely cases of mild preeclampsia (a non-evidence indication) in that particular group (the exact number could not be calculated due to retrospective

character of the analysis). Nevertheless, preeclampsia in our setting appeared to be a major factor increasing the risk of adverse neonatal outcome with OR 5.01. It is difficult to state whether it was due to its severity, or too early induction. Barton et al. reviewed the data on late preterm births of pregnancies complicated by gestational hypertension [17]. It appeared that deliveries induced  $<37$  weeks of gestation resulted in increased neonatal morbidity with no maternal benefit. Another recent clinical trial regarding pregnancies with mild preeclampsia and gestational hypertension revealed that expectant management and labor induction after 37 weeks improved maternal outcomes [18]. Nevertheless, the cited papers did not evaluate twin pregnancies alone.

IUGR was the second most frequent indication in our study (17%) - all cases were accompanied by abnormal testing or inadequate growth, therefore, were evidence-based. Intrahepatic cholestasis of pregnancy, which accounted for 9.75% of labor inductions in our material, did not always present with bile acid concentration  $>40\mu\text{mol/L}$  (only around 40%), so it might be considered one of the potentially avoidable indications.

There are various differences among institutions and countries regarding certain indications. The major concern, though, should be those deliveries where there are no clear indications whatsoever and still an invasive medical management is undertaken. In our study uncertain indications for late preterm induction reached 14.63%, which definitely requires careful evaluation in the future. On the other hand, some authors even state that current evidence based knowledge does not allow a safe reduction of late preterm births [19, 20]. A common problem in the obstetric ward is to decide whether preterm birth  $>34$  weeks of gestation is a better choice than continuing complicated pregnancy. Unequivocal answer does not exist, as no well-designed prospective studies have been performed so far.

Only few researches discuss the rates of different neonatal complications in late preterm babies, mostly among singletons. Consortium on Safe Labor reported a 5.2% rate of respiratory distress syndrome in LPTB infants, proving that it remains the most common and significant case of respiratory morbidity in that particular group. According to the literature TTN (transient tachypnea of the newborn) – not included as our primary outcome - is the second most common respiratory disorder, with the rate of 4% [21]. According to Gouyon et al. the rate of severe respiratory disorders requiring mechanical ventilation and/or CPAP among LPTB infants was 8.3% in comparison to less than 1% among term babies [22]. Refuerzo et al. reported significantly higher rates of respiratory complications among LPTB newborns – 11.7% of RDS, 20.8% of TTN, 6.2% of mechanical ventilation and as much as 30.3% of oxygen supplementation [3]. The rate of NICU admission in their study was very high – it reached 54% among LPT infants with the average NICU stay of 12.4+-14.7 days. In our study the rate of respiratory disorders requiring mechanical ventilation and/or CPAP was 15.94% in SLP, but it reached 41.46% in ILP. NICU admission analysis revealed similar findings: 14.49% in SLP and 31.71% in ILP.

The prevalence of other neonatal complications among late preterm newborns varies greatly among researchers and countries: the rate of NEC varies from 0% to 4.8%, IVH 8.1%, sepsis from 2.2% to 7.2% and the rate of jaundice requiring phototherapy reaches 34.8% [3, 8, 22].



In our study the rates of other complications did not differ between SLP and ILP and the rates were concordant with the literature. Only the rates of intraventricular hemorrhage in our study seem high (26% and 17%), which is probably due to the fact, that IVH grade 2 was also included in the results.

Nevertheless, the problems of incomplete fetal maturation, such as hypothermia, jaundice or feeding difficulties still require different approach [20]. Perinatal care worldwide should therefore focus on prevention of non-indicated interventions in preterm population.

## Conclusions

Late prematurity in twin pregnancies is associated with higher risk of neonatal morbidity than in term twins. Iatrogenic late preterm birth increases the risk of NICU admission and respiratory disorders in neonates in comparison to spontaneous late preterm birth. Despite the fact that respiratory complications are generally mild and mostly temporary, there is a need for careful evaluation of indications for delivery in that particular group.

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